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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,346	09/23/2005	Fabrice Le Gall	03528.0146.PCUS00	7228

27194 7590 04/01/2010

HOWREY LLP-CA
C/O IP DOCKETING DEPARTMENT
2941 FAIRVIEW PARK DRIVE, SUITE 200
FALLS CHURCH, VA 22042-2924

EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
04/01/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,346	LE GALL ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,16,17 and 21-27* is/are pending in the application.

4a) Of the above claim(s) *14,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-7-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed January 7, 2010 have been considered.

   Claims 14, 16, 17 and 21-27 are pending.

   Claims 21-27 are under examination.

   Claims 14, 16 and 17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 6, 2008.

2. The prior rejections of record can be found in the Office Action mailed July 9, 2009.

   The previous rejection under 35 USC 112, 1st paragraph has been withdrawn in view of applicant's amendment to the claims.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

   (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 21, 23 and 25 stand rejected and new claims 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (WO 9847531) in view of Hsu et al. (Transplantation. 1999 Aug 27;68(4):545-54), Holliger et al. (5,837,242) and Chapman et al. (Nat Biotechnol. 1999 Aug;17(8):780-3), essentially for the reasons of record as put forth in the prior Office Action mailed July 9, 2009 and for the reasons given below.

   Arguments against the prima facie case of unpatentability

   Applicant argues the teachings of Smith suggest the use of anit-CD3 antibodies as an immunosuppressant is unpredictable, that while Holliger teaches anti-CD3 diabodies, the anti-CD3 diabodies of Holliger are only taught in the context of "T cell activation" and that one of ordinary skill in the art would not have been motivated to make an anti-CD3 diabody

because one of ordinary skill in the art would not have recognized an advantage of an anti-CD3 diabody over the anti-CD3 F(ab')2 antibody taught by Smith.

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Actions mailed July 9, 2009 and October 3, 2008.

With respect to Smith, applicant argues that Smith's description of the mechanism by which various anti-CD3 antibodies act as immunosuppressants is complex and therefore the teachings of Smith are "not necessarily indicative of any other CD3-binding molecules." (see remarks page 5, last paragraph).

Applicant's arguments are not found convincing because while Smith describes how anti-CD3 antibodies having a functional FcR binding domain, e.g., the anti-CD3 antibody OKT3, have different effects on T cells than anti-CD3 antibodies having a low-functioning or non-existent FcR binding domain, e.g., anti-CD3-IgG3 or an anti-CD3 F(ab')2 fragment, contrary to applicant's argument the teachings of Smith are unambiguous that the genus of FcR-low or nonbinding anti-CD3 antibodies are useful in the treatment of autoimmune diseases and graft rejection (see the teachings of Smith put forth on pages 7-8 of the Office Action mailed October 3, 2008).

With respect to Holliger, applicant's argument has three parts:

I. Applicant argues "Holliger discloses diabodies that have a rigid structure and a back to back position of the binding sites…Holliger further teaches cross-linking the CD3 antigen so as to activate T cells (Col. 22, lines 15-16)…It is noted that Holliger always assumes that the T cells will be activated through the action of the diabodies." (see remarks page 6, 2nd paragraph, applicant's emphasis shown).

II. Applicant further makes a number of assertions related to the ability of a diabody to cross-linking CD3 on the surface of a T cell versus its ability to interact with CD3 on the surface of a T cell and either CD3 on another T cell or presumably some non-CD3 antigen on a wholly different cell like a B cell (see remarks page 6, 3rd paragraph).

III. Applicant concludes, "Therefore, Holliger does not indicate that an anti-CD3 diabody may act as an immunosuppressant. To the contrary, Holliger only teaches that T cells will be activated by the diabodies. Considering that Smith emphasizes the modulation of CD3 is highly complex and different antibodies have different mechanisms of action, and that not any immunosuppressive activity was indicated for diabodies, one skilled in the art would not have been motivated to select an anti-CD3 diabody as an alternative for F(ab')2 fragments as an immunosuppressant."

Applicant's argument has been considered but has not found convincing for a number of reasons.

As to the first part of applicant's argument, it is the examiner's position that applicant is narrowly construing the teachings of Holliger to fit their argument rather than considering them through the lens of one of ordinary skill in the art as of applicant's date of invention.

The teachings of Holliger applicant refers to in their argument regarding cross-linking the CD3 antigen so as to activate T cells are reproduced below: "The diabodies may also bind simultaneously to two epitopes on the same surface, for example a viral coat, so as to bind with high avidity and to block the uncoating of the virus; or by cross-linking the CD3 antigen so as to activate T-cells."

One of ordinary skill in the art would understand this teaching to mean that an anti-CD3 diabody by cross-linking CD3 molecules on the surface of a T cell can activate said T cell. As put forth in the previous Office Action mailed July 9, 2009 at page 4, 5th paragraph, in the context of the teachings of Smith the ability of an anti-CD3 antibody to bridge two CD3 on the T-cell surface and deliver a partial signal was known to be essential for its ability to immunomodulate the Th1/Th2 cytokine balance in favor of Th2. Thus, one of ordinary skill in the art would not consider the teachings of Smith and Holliger to be inconsistent as implied by applicant's argument. Rather one of ordinary skill in the art would consider Holliger as teaching that a CD3 diabody can bind simultaneously to two epitopes on the surface of a T cell so as to activate said T-cell, a function consistent with the ability of other antibodies that cross-link CD3 on the surface of a T cell, such as an OKT3 F(ab')2 fragment, and in so doing activate T cell immunomodulation.

As to the second part of applicant's argument, first it is noted that arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984), See MPEP § 2145.

Secondly, the meaning of much of applicant's assertions are unclear. For example, the meaning of the following assertion is unclear: "There appears to be no essential difference between cross-linking CD3 on the T cell surface by a diabody that binds to CD3 on a T-cell at one end and that binds to either a B-lymphocyte or another T-cell at the other end. It would certainly not have been surprising in view of the above facts if a stronger T cell activation had been obtained when the CD3 molecules were cross-linked by T-cell bridging rather than T-cell-B-lymphocyte bridging."

If there is "***no essential difference*** between cross-linking CD3 on the T cell surface by a diabody that binds to CD3 on a T-cell at one end and that ***binds to either a B-lymphocyte or another T-cell at the other end***" then why would it "***certainly not have been surprising*** in view of the above facts ***if a stronger T cell activation*** had been obtained when the CD3 molecules were cross-linked by ***T-cell bridging rather than T-cell-B-lymphocyte bridging***?" (emphasis added). Isn't this an essential difference between these asserted scenarios? Moreover, what is the relevance of these assertions to the prima facie case of unpatentability?

As to the last part of applicant's argument, applicant's conclusion that "one skilled in the art would not have been motivated to select an anti-CD3 diabody as an alternative for F(ab')2 fragments as an immunosuppressant," leads to applicant's last arguments concerning the teachings of the art with respect to making F(ab')2 fragments as taught by Smith. (see Remarks page 7).

Applicant's argument that the prior art recognizes F(ab')2 can be produced in bacteria is acknowledged and is found convincing.

Nonetheless, this does not make the claimed invention non-obvious. For the reasons given above one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of successfully making ***either*** an OKT3-based anti-CD3 F(ab')2 fragment or an OKT3-based anti-CD3 diabody. The art does not have to teach that an OKT3-based anti-CD3 diabody is markedly superior to an OKT3-based anti-CD3 F(ab')2 fragment to render the claimed invention obvious. It is also worth noting that as put forth in the previous non-final Office Action mailed October 3, 2008 at page 9, 5th paragraph (emphasis added): "***Importantly, both anti-CD3 diabody and anti-CD3 F(ab')$_2$ antibodies are devoid of the antibody constant regions*** which mediate FcR cross-linking, thus one of ordinary skill in the art ***would have been motivated to make and use such molecules for therapeutic uses vs. a whole anti-CD3*** antibody since the caveats associated with attempting to inhibit FcR cross-linking through point mutagenesis of antibody Fc are not an issue. Additionally, as taught by Chapman, compared to whole antibodies, antibody fragments allow for decreased cost and time to production so this is an additional motivation one of ordinary skill in the art would have for making, for example, an anti-CD3 diabody vs. a whole antibody containing a mutation in the Fc region that inhibits FcR cross-linking."

Arguments concerning "unexpected and superior immunosuppression effect of diabody"

Applicant presents a Declaration by Dr. Melvin Little, one of the co-inventors of the instant application which shows data comparing an OKT3-based diabody with an OKT3-based tandem antibody with the OKT3 anti-CD3 antibody itself. Dr. Little's Declaration concludes: "The above experiments demonstrate that an anti-CD3 diabody according to the above referenced patent application did not induce any T cell proliferation, whereas a tandem diabody TandAb induced a significant T cell response. It is noted that both antibodies are devoid of constant domains and are composed of the identical CD3 specific domains. That is, it is unexpected that an anti-CD3 diabody according to the above-referenced patent application exhibited a significant immunosuppression effect, and that such effect was superior over prior art-known diabody TandAb."

Based on this declaration applicant argues "Smith teaches that F(ab')2 fragments lacking the Fc domain exhibited significantly reduced T cell activation and fewer side effects (page 50, 1" full paragraph). This is confirmed by the TandAb which lacks an Fc domain and induced

a significant lower cell proliferation than the OKT3 (see Fig. 1 of the declaration). However, it could not be expected that a cell proliferation can be avoided by the instantly claimed diabody. Such property of extremely low immunogenicity of the instantly claimed diabody is a marked improvement over the TandAb or the OKT3, which provides the practical advantage of allowing administration of the instantly claimed diabody at higher dosages and repeated times."

The Declaration by Dr. Melvin Little and applicant's argument in conjunction therewith have been considered but have not been found convincing.

As stated in the previous Office Action at page 4, 2nd paragraph, "...applicant fails to compare the claimed invention to the nearest prior art which could be any ***divalent*** OKT3 derived anti-CD3 antibody lacking an Fc domain, such as OTK3 derived $F(ab')_2$ or bivalent $(Fab'zipper)_2$." This is still the case because the TandAb is a ***tetravalent*** anti-CD3 not a ***bivalent*** CD3.

Moreover, contrary to applicant's argument, it "could ~~not~~ be expected that a cell proliferation can be avoided by the instantly claimed diabody" when the claimed antibody is compared to the nearest prior art. For example, one of ordinary skill in the art if asked to compare the teachings of Woodle et al. (Transplantation. 1991 Aug;52(2):354-60) at page 357, Figure 3 with the teachings of the instant specification would conclude the an OKT3-based $F(ab')_2$ and an OKT3-based diabody likely have the same or substantially the same ability to not induce PBMC proliferation (compare the PBMC proliferative effect of the Woodle OKT3 $F(ab')_2$ at 10^3 ng/mL antibody in Figure 3, which based on a molecular weight of appx. 102 kD/mole is approximately the same as $1x10^5$ pM OKT3 $F(ab')_2$ to the proliferative effect of the OKT3 diabody at the same molar concentration in Figure 1 of Dr. Little's declaration.

One of ordinary skill in the art would not have found the increased proliferative effect of the tetravalent TandAb over the bivalent diabody surprising because one of ordinary skill in the art would expect a molecule with four rather than two CD3 binding sites to have a greater ability to cross-link cell surface CD3 molecules and activate T cell proliferation.

New claims 26 and 27

Smith teaches pharmaceutical compositions of antibodies reactive with CD3 are formulated with "standard, well-known nontoxic physiologically acceptable carriers, adjuvants, and vehicles as desired." (see page 56, Section VIII). While Smith does not mention that the pharmaceutical carrier should be sterile, it has been recognized in the medical arts since their infancy that the sterility of pharmaceutical compositions and medicaments is of the utmost importance given that bacteria and viruses found in non-sterile solutions cause sickness and further given the well known medical maxim "first, do no harm."

In conclusion, when Applicant's arguments and the evidence of the instant specification are taken as a whole and weighed against the evidence supporting the *prima facie* case of unpatentability, the instant claims, by a preponderance of evidence, remain unpatentable. See M.P.E.P. § 716.01(d).

Thus, the instant claims stand rejected as unpatentable over Smith in view of Hsu, Holliger and Chapman.

5. Claims 22 and 24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (WO 9847531) in view of Hsu et al. (Transplantation. ii October 3, 2008)), Holliger et al. (5,837,242) and Chapman et al. (Nat Biotechnol. 1999 Aug;17(8):780-3) as applied to claims 21, 23 and 25 above, and further in view of Kipriyanov et al. (Protein Eng. 1997 Apr;10(4):445-53), for the reasons of record as put forth in the prior Office Action mailed July 9, 2009.

Applicant argues Kipriyanov does not cure the deficiencies of the Smith, Hsu, Holliger or Chapman references.

Applicant's arguments have been considered, but have not been found convincing, because as described above claims 21, 23 and 25 are unpatentable over Smith, Hsu, Holliger and Chapman for the reasons of record, and applicant has not convincingly argued why the further addition of Kipriyanov would not render the instant claims unpatentable as well.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claims stand unpatentable over Smith in view of Hsu, Holliger, Chapman and Kipriyanov.

A New Grounds of Rejection is put forth below.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 21 is rejected under 35 U.S.C. 102(b) as anticipated by Holliger (5,837,242).

Holliger teaches making an anti-CD3 diabody that can activate T cells (Col. 22, lines 12-16).

Note that these teachings of Holliger are echoed in applicant's arguments found on page 6, 2nd and 4th paragraphs of their remarks filed January 7, 2010: "[h]olliger further teaches cross-linking the CD3 antigen so as to activate T cells (Col. 22, lines 15-16). It is noted that Holliger always assumes that the T cells will be activated through the action of the diabodies," and "[t]herefore, Holliger does not indicate that an anti-CD3 diabody may act as an immunosuppressant. To the contrary, Holliger only teaches that T cells will be activated by the diabodies."

8. Claims 21 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holliger (5,837,242).

Holliger teaches making an anti-CD3 diabody that can activate T cells (Col. 22, lines 12-16). Holliger also teaches pharmaceutical and medicaments comprising anti-CD3 diabodies (see Col. 8, lines 31-34).

However, Holliger does not teach that pharmaceutical and medicaments comprising anti-CD3 diabodies should comprise a suitable pharmaceutical carrier such as a sterile solution.

Nonetheless, it has been recognized in the medical arts since their infancy that the sterility of pharmaceutical compositions and medicaments is of the utmost importance given that bacteria and viruses found in non-sterile solutions cause sickness and further given the well known medical maxim "first, do no harm."

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Examiner, Art Unit 1644